

all outstanding rejections in the Office Action mailed on June 11, 1996, in view of the following remarks.

IN THE CLAIMS:

Please cancel claims 10, 12, 14, 17, 18, and 22 without prejudice or disclaimer.

Please amend the claims as follows:

2. (Amended) [DNA coding for a secretable TNF-binding protein, having the formula] DNA according to claim 61, wherein said DNA comprises the sequence:

R² GAT AGT GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA
AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC
TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC
AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC
CTC AGA CAC TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG
GGT CAG GTG GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC
GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT
GAA AAC CTT TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT
GGG ACC GTG CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG
TGC ACC TGC CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT
GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG
TTG TGC CTA CCC CAG ATT GAG AAT

wherein R² is [optionally] absent or [represents] is a DNA comprising a sequence coding for a polypeptide which can be cleaved *in vivo*, or a fragment or degenerate variant thereof.

3. (Amended) DNA according to claim 2, [coding for secretable TNF binding protein,] wherein R² [represents] is a DNA comprising a sequence which codes entirely or partly for a signal sequence.

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4. (Amended) DNA according to claim 2, [characterized in that] wherein R²
[has the formula] is a DNA comprising the sequence CTG GTC CCT CAC CTA GGG
GAC AGG GAG AAG AGA or a fragment thereof.

5. (Amended) DNA according to claim 3, [characterized in that] wherein R²
[represents] is a DNA comprising the sequence R³ CTG GTC CCT CAC CTA GGG GAC
AGG GAG AAG AGA, wherein R³ [represents] is a DNA coding for a signal peptide, or a
fragment thereof.

6. (Amended) DNA according to claim 5, [characterized in that] wherein R³
[represents] is a DNA comprising the sequence:

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA, or
or a fragment thereof.

7. (Twice Amended) A nucleic acid coding for a polypeptide having the ability
to bind TNF which hybridizes with DNA complementary to the DNA defined in claim 1
under conditions of low stringency [and which codes for a polypeptide having the ability
to bind TNF].

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Claim 9, line 4, "after" or a" insert --fragment or--; and

line 5, after "fragment" insert --thereof--.

11. (Amended) A [recombinant DNA molecule] vector designated pADTNF-BP,
pADBTNF-BP, pADTNF-R, or pADBTNF-R.

Please add the following new claims 27-61:

--27. DNA coding for a polypeptide having the ability to bind TNF selected from
the group consisting of:

A) a polypeptide comprising the amino acid sequence:

met	gly	leu	ser	thr	val	pro	asp	leu	leu	leu	pro	leu	val
leu	leu	glu	leu	leu	val	gly	ile	tyr	pro	ser	gly	val	ile
gly	leu	val	pro	his	leu	gly	asp	arg	glu	lys	arg	asp	ser
val	cys	pro	gln	gly	lys	tyr	ile	his	pro	gln	asn	asn	ser
ile	cys	cys	thr	lys	cys	his	lys	gly	thr	tyr	leu	tyr	asn
asp	cys	pro	gly	pro	gly	gln	asp	thr	asp	cys	arg	glu	cys
glu	ser	gly	ser	phe	thr	ala	ser	glu	asn	his	leu	arg	his
cys	leu	ser	cys	ser	lys	cys	arg	lys	glu	met	gly	gln	val
glu	ile	ser	ser	cys	thr	val	asp	arg	asp	thr	val	cys	gly
cys	arg	lys	asn	gln	tyr	arg	his	tyr	trp	ser	glu	asn	leu
phe	gln	cys	phe	asn	cys	ser	leu	cys	leu	asn	gly	thr	val
his	leu	ser	cys	gln	glu	lys	gln	asn	thr	val	cys	thr	cys
his	ala	gly	phe	phe	leu	arg	glu	asn	glu	cys	val	ser	cys
ser	asn	cys	lys	lys	ser	leu	glu	cys	thr	lys	leu	cys	leu
pro	gln	ile	glu	asn	val	lys	gly	thr	glu	asp	ser	gly	thr
thr	val	leu	leu	pro	leu	val	ile	phe	phe	gly	leu	cys	leu
leu	ser	leu	leu	phe	ile	gly	leu	met	tyr	arg	tyr	gln	arg
trp	lys	ser	lys	leu	tyr	ser	ile	val	cys	gly	lys	ser	thr
pro	glu	lys	glu	gly	glu	leu	glu	gly	thr	thr	thr	lys	pro
leu	ala	pro	asn	pro	ser	phe	ser	pro	thr	pro	gly	phe	thr
pro	thr	leu	gly	phe	ser	pro	val	pro	ser	ser	thr	phe	thr
ser	ser	ser	thr	tyr	thr	pro	gly	asp	cys	pro	asn	phe	ala

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ala pro arg arg glu val ala pro pro tyr gln gly ala asp
pro ile leu ala thr ala leu ala ser asp pro ser pro tyr gln gly ala pro asp
pro leu gln lys trp glu asp ser ala his lys pro ile pro gln ser
leu asp thr asp asp pro ala thr leu tyr ala val glu val
asn val pro pro leu arg trp lys glu phe val arg gln asp
gly leu ser asp his glu ile asp arg leu glu leu
gly arg cys leu arg glu ala gln tyr ser met leu ala thr
trp arg arg arg thr pro arg arg glu ala thr leu glu leu
leu gly arg val leu arg asp met asp leu leu gly cys leu
glu asp ile glu ala leu cys gly pro ala ala pro
pro ala pro ser leu arg;

B) a polypeptide comprising the amino acid sequence:

asp ser val cys pro gln gly lys tyr ile his pro gln asn
asn ser ile cys cys thr lys cys his lys gly thr tyr cys leu
tyr asn asp cys pro gly pro gly gln asp thr asp cys arg
glu cys glu ser gly ser phe thr ala ser glu asn his leu
arg his cys leu ser cys ser lys cys arg lys glu met gly
gln val glu ile ser ser cys thr val asp arg asp thr thr val
cys gly cys arg lys asn gln tyr arg his tyr trp
ser glu asn leu phe gln cys phe asn cys ser leu cys leu
asn gly thr val his leu ser cys gln glu lys gln asn thr
val cys thr cys his ala gly phe leu arg glu asn asn glu
cys val ser cys ser asn cys lys ser leu glu cys threonine
lys leu cys leu pro gln ile glu asn; and

C) a fragment or functional derivative of A or B.

28. A DNA according to claim 27, wherein said polypeptide is selected from the group consisting of:

a polypeptide comprising the amino acid sequence:

R₂ asp ser val cys pro gln gly lys tyr ile his pro gln asn
asn ser ile cys cys thr lys cys his lys gly thr tyr cys leu
tyr asn asp cys pro gly pro gly gln asp thr asp cys arg

glu cys glu ser gly ser phe thr ala ser glu asn his leu
arg his cys leu ser cys ser lys cys arg lys glu met gly
gln val glu ile ser ser cys thr val asp arg trp asp thr val
cys gly cys arg lys asn gln tyr arg his tyr leu cys leu
ser glu asn leu phe gln cys phe asn cys ser leu cys leu
asn gly thr val his leu ser cys gln glu lys gln asn thr
val cys thr cys his ala gly phe leu arg glu asn glu
cys val ser cys ser asn cys lys lys ser leu glu cys thr
lys leu cys leu pro gln ile glu asn;

wherein R₂ is absent or is a polypeptide which can be cleaved *in vivo*; and

a fragment or functional derivative thereof which binds TNF.

29. A DNA according to claim 28, wherein said polypeptide includes at least one additional amino acid at the amino-terminus, at the carboxyl-terminus, or at both the amino-terminus and at the carboxyl-terminus.

30. A DNA according to claim 29, wherein said polypeptide includes at least one additional amino acid at the amino-terminus and at the carboxyl-terminus.

31. A DNA according to claim 29, wherein said polypeptide includes at least one additional amino acid at the amino-terminus.

32. A DNA according to claim 31, wherein said polypeptide includes a methionine at the amino-terminus.

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33. A DNA according to claim 29, wherein said polypeptide includes at least one additional amino acid at the carboxyl-terminus.

34. A nucleic acid that hybridizes to a DNA complementary to the DNA defined in claim 28 under conditions of low stringency and which codes for a polypeptide having the ability to bind TNF.

35. A vector comprising a DNA sequence which codes for a TNF binding protein which binds TNF.

36. A vector comprising a DNA sequence defined in claim 28.

37. A vector according to claim 36, which is replicable in a prokaryotic and/or a eukaryotic host cell.

38. A vector according to claim 37, which is replicable in a prokaryotic cell.

39. A vector according to claim 38, wherein said DNA sequence includes ATG at the amino terminus.

40. A vector according to claim 38, which is replicable in *Escherichia coli*.

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41. A vector according to claim 37, which is replicable in a eukaryotic cell.

42. A vector according to claim 41, which is replicable in a mammalian cell.

43. A vector according to claim 42, which is replicable in a Chinese Hamster Ovary cell.

44. A vector according to claim 42, which is replicable in a COS cell.

45. A host cell containing a recombinant DNA molecule comprising a DNA sequence defined in claim 28.

46. A host cell according to claim 45, which is a prokaryotic cell.

47. A host cell according to claim 46, which is *Escherichia coli*.

48. A host cell according to claim 45, which is a eukaryotic cell.

49. A host cell according to claim 48, which is a mammalian cell.

50. A host cell according to claim 49, which is a Chinese Hamster Ovary cell.

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51. A host cell according to claim 49, which is a COS cell.

52. A recombinant host cell containing a DNA molecule comprising a DNA sequence defined in claim 28.

53. A recombinant host cell according to claim 52, wherein the DNA molecule comprises promoter DNA, other than the promoter DNA for the native polypeptide having the ability to bind TNF, operatively linked to the DNA sequence defined in claim 28.

54. A process for preparing a polypeptide having the ability to bind TNF comprising producing the polypeptide in a recombinant host cell according to claim 52 under suitable conditions to express the DNA molecule contained therein to produce the polypeptide.

55. A process for preparing a polypeptide having the ability to bind TNF comprising producing the polypeptide in a recombinant host cell according to claim 53 under suitable conditions to express the DNA molecule contained therein to produce the polypeptide.

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56. A process according to claim 55, further comprising harvesting the expressed recombinant polypeptide.

57. A process according to claim 56, further comprising a step of modifying the harvested recombinant polypeptide, wherein the modified polypeptide possesses TNF inhibitory activity.

58. A process according to claim 57, wherein said step of modifying the harvested recombinant polypeptide comprises chemically derivatizing the harvested polypeptide.

59. A process according to claim 57, further comprising a step of combining the modified recombinant polypeptide with pharmaceutically acceptable carrier to form a pharmaceutical composition.

60. A process according to claim 54, wherein said recombinant DNA molecule is contained in an expression vector.

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61. DNA coding for a polypeptide having the ability to bind to TNF, wherein said DNA coding said polypeptide is selected from the group consisting of:

A) DNA comprising the sequence:

ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG CTG CCA CTG GTG
CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT
GGA CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT
GTG TGT CCC CAA GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG
ATT TGC TGT ACC AAG TGC CAC AAA GGA ACC TAC TTG TAC AAT
GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC TGC AGG GAG TGT
GAG AGC GGG TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC
TGC CTC AGC TGC TCC AAA TGC CGA AAG GAA ATG GGT CAG GTG
GAG ATC TCT TCT TGC ACA GTG GAC CGG GAC ACC GTG TGT GGC
TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG AGT GAA AAC CTT
TTC CAG TGC TTC AAT TGC AGC CTC TGC CTC AAT GGG ACC GTG
CAC CTC TCC TGC CAG GAG AAA CAG AAC ACC GTG TGC ACC TGC
CAT GCA GGT TTC TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT
AGT AAC TGT AAG AAA AGC CTG GAG TGC ACG AAG TTG TGC CTA
CCC CAG ATT GAG AAT GTT AAG GGC ACT GAG GAC TCA GGC ACC
ACA GTG CTG TTG CCC CTG GTC ATT TTC TTT GGT CTT TGC CTT
TTA TCC CTC CTC TTC ATT GGT TTA ATG TAT CGC TAC CAA CGG
TGG AAG TCC AAG CTC TAC TCC ATT GTT TGT GGG AAA TCG ACA
CCT GAA AAA GAG GGG GAG CTT GAA GGA ACT ACT ACT AAG CCC
CTG GCC CCA AAC CCA AGC TTC AGT CCC ACT CCA GGC TTC ACC
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TCC ACC TTC ACC
TCC AGC TCC ACC TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG
GCT CCC CGC AGA GAG GTG GCA CCA CCC TAT CAG GGG GCT GAC
CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC CCC AAC
CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC
CTA GAC ACT GAT GAC CCC GCG AGC CTG TAC GCC GTG GTG GAG
AAC GTG CCC CCG TTG CGC TGG AAG GAA TTC GTG CGG CGC CTA
GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG GAG CTG CAG AAC
GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC
TGG AGG CGG CGC AGC CCG CGG CGC GAG GCC AGC CTG GAG CTG
CTG GGA CGC GTG CTC CGC GAC ATG GAC CTG CTG GGC TGC CTG
GAG GAC ATC GAG GAG GCG CTT TGC GGC CCC GCC GCC CTC CCG
CCC CGC CCC AGT CTT CTC AGA TGA

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